1623

CASE LD0226 (NP)

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Maureen S. Gibbons		July 26, 2004
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF MINOTTI ET AL.

APPLICATION NO: 09/954,953 Art Unit: 1623

FILED: SEPTEMBER 18, 2001 Examiner: Devesh Khare

FOR: METHOD FOR REDUCING TOXICITY OF COMBINED CHEMOTHERAPIES

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO OFFICE ACTION

This is in response to the Office Action dated April 16, 2004 regarding the above-mentioned patent application. Claims 15-17 are currently pending.

REMARKS
35 U.S.C. § 103 (a)

Claims 15 and 16 stand rejected as allegedly obvious over U.S. Pat. No. 5,908,835 (Bissery) in view of Loshak (XP-002222026: DG Dispatch-ECCO Sept. 17, 1999). The Bissery patent teaches compositions comprising taxol, taxotere, and their derivatives described in column 1, lines 13 to 16, in combination with anthracylines, such as doxorubicin. The Losak reference describes methods for treating breast cancer with Taxol and doxorubicin. The present invention, on the other hand, is directed to compositions comprising chemotherapeutic combinations of 4-desacety-4-methylcarbonate and doxorubicin.

The Office Action fails to provide any evidence that one skilled in the art would be motivated to modify the cited references in a manner that would result in the present invention. The test for obviousness is whether the claimed invention would have been

obvious to one of ordinary skill in the art at the time of the invention, and not whether the claimed invention was "obvious to try." *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81 (Fed. Cir. 1986). There is no reason to believe that one skilled in the art would be motivated to make the presently claimed combinations, based on the cited references alone. In fact, it is only with the benefit of hindsight provided by the present disclosure that one skilled in the art would be motivated to practice the specifically claimed combinations which have a reduced ability to stimulate formation of cardiotoxic by-products relative to compositions consisting of paclitaxel and doxorubicin or docetaxel and doxorubicin.

In support of the rejection, at page 4, the Examiner suggests that because taxol and 4-desacetyl-4-methylcarbonate taxol have the same core, "the skilled artisan would expect these compounds to have similar properties." However, as Applicants have demonstrated, the taxane derivative of the present invention in combination with doxorubicin does not have a cardiotoxic profile that is similar to the cardiac profile of taxol or docetaxel in combination with doxorubicin, despite having a similar core. Applicants have shown that 4-desacetyl-4-methylcarbonate does not enhance the conversion of doxorubicin to potentially toxic metabolites or by-products. Thus, 4-desacetyl-4-methylcarbonate offers potential advantages over taxol in terms of cardiac safety when administered to patients in combination with anthracyclines.

In the absence of evidence tending to show that one skilled in the art would have been motivated to select the specific taxane derivative that is described in the present invention, out of all the hundreds of taxane derivatives available, for combination with doxorubicin to provide chemotherapeutic compositions having improved safety profiles, a *prima facie* case of obvious is not established. Accordingly, Applicants request withdrawal of the rejection.

Applicants believe that the present claims are in condition for allowance. An early Office Action to that effect is therefore, earnestly solicited.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-3453

Date: July 26, 2004

Maureen S. Gibbons
Attorney for Applicants
Reg. No. 44,121